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Chronic Renal Failure

Its Effect on Calcium, Phosphorus and Osseous Metabolism; A Unified Approach

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• **The renal osteodystrophies represent the metabolic consequences of (1) vitamin D resistance, (2) secondary hyperplasia of the parathyroids, and (3) the changes in serum $PO_4^{\equiv}$ and Ca^{++} secondary to the renal insufficiency per se.**

The osseous lesion in any given patient with chronic renal failure may be osteitis fibrosa, rickets (osteomalacia), calcium deficiency osteoporosis or any combination of these. The concentration of Ca^{++} and $PO_4^{\equiv}$ in the serum is determined by the degree of renal failure and the skeletal response to parathyroid hormone.

CHRONIC RENAL DISEASE, accompanied by progressive destruction of nephron mass and azotemia, frequently causes hypocalcemia, hyperphosphatemia and osseous disorders. The latter, referred to as renal osteodystrophy, consist of retardation of growth and dwarfism, osteitis fibrosa, rickets or osteomalacia, or rarely osteosclerosis. Stanbury and coworkers recently classified these disorders and described their symptomatology in excellent reviews.[9,10] Physicians who care for large numbers of children or adults with chronic renal failure are impressed by the lack of correlation between the levels of calcium and inorganic phosphorus in the serum and between these biochemical changes and the osseous pathologic changes. Similarly, therapy directed toward a correction of these abnormalities —alkali administration, high calcium diets and phosphate-binding in the gastrointestinal tract with aluminum hydroxide gels—has frequently been unsuccessful.

It is hoped that the following scheme will contribute to a better understanding of the deranged calcium, phosphorus and osseous metabolism in chronic renal failure and to its therapy. The scheme is based on the following observations.*

1. The parathyroid glands are stimulated by a reduction in the level of free calcium ion (Ca^{++}) in the body fluids (and questionably a rise in serum phosphorus per se).

2. Parathyroid hormone regulates the level of Ca^{++} in the body fluids by (a) enhancing the liberation of skeletal calcium, (b) increasing the renal clearance of phosphorus, and (c) *decreasing* the renal clearance of Ca^{++}.[1,7,12]

3. For any given level of parathyroid activity, a rise in the concentration of inorganic phosphorus

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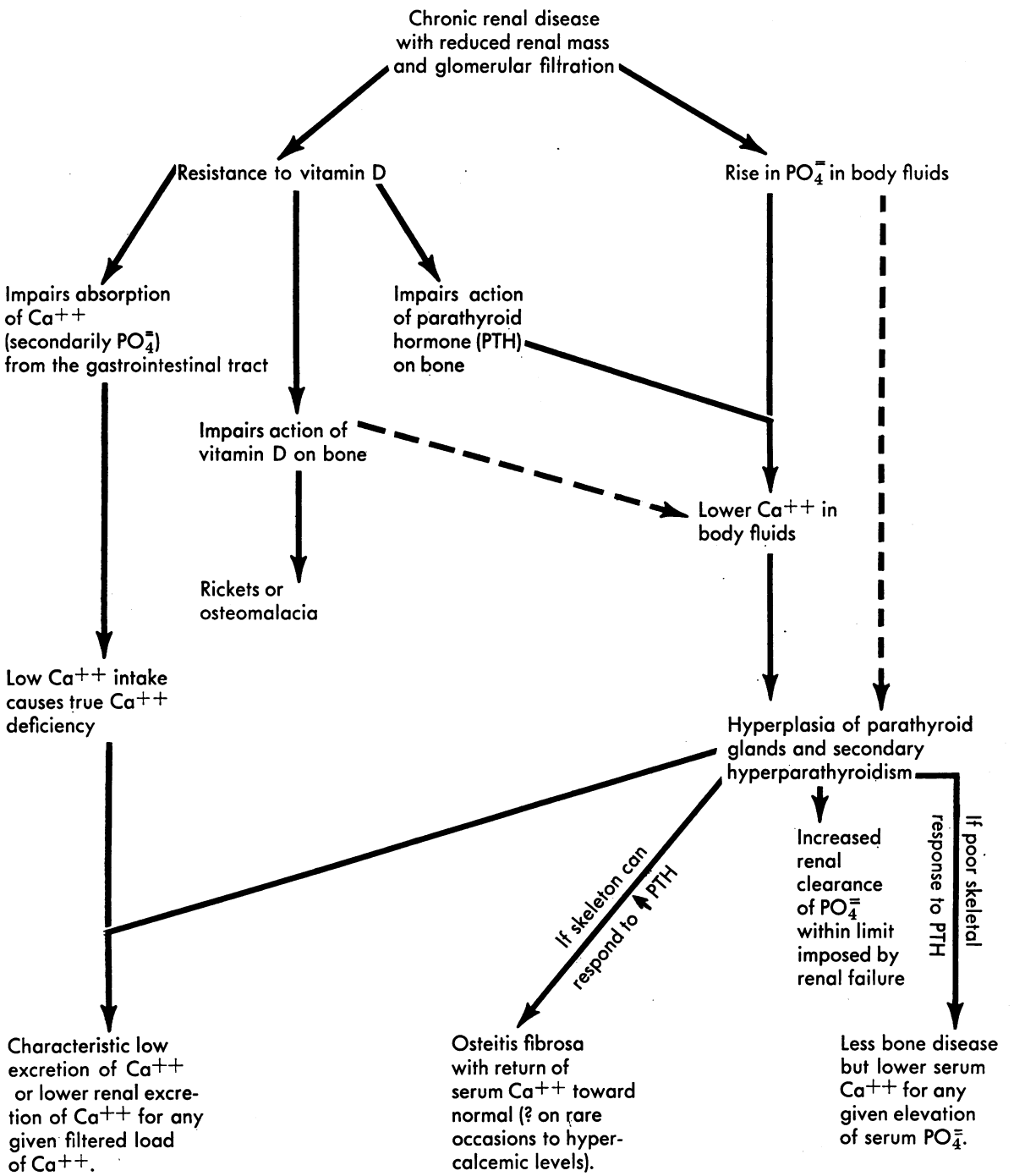
*References have been included for those observations derived from recent investigations. It is reasonable to consider these as still tentative.

CHART 1. CALCIUM AND PHOSPHORUS METABOLISM IN CHRONIC RENAL FAILURE



The final bone lesion may be osteitis fibrosa, rickets (osteomalacia), calcium deficiency osteoporosis, or any combination of these. This scheme does not explain the rare case of osteosclerosis (increased density of bone) seen in chronic renal disease.

in the body fluids causes a decrease in the concentration of Ca^{++}. This results from a shift of Ca^{++} into the skeleton and the establishment of a new dynamic equilibrium with a higher serum $PO_4^{\equiv}$ and lower Ca^{++} concentration.

4. Vitamin D deficiency or resistance to this vitamin impairs the action of parathyroid hormone on the skeleton[2,6,8]—that is, in the absence of an effect of vitamin D on the skeleton, greater than normal amounts of parathyroid hormone are necessary to maintain the Ca^{++} concentration in body fluids.

5. Vitamin D deficiency causes secondary hyperplasia of the parathyroid glands.

6. Pronounced resistance to vitamin D exists in patients with chronic renal failure.[4,9,10]

7. Secondary hyperplasia of the parathyroid glands accompanies chronic renal failure.

Chronic renal disease, at some stage in its development (the duration is unknown), causes an increased resistance to the action of vitamin D on the gastrointestinal tract and the skeleton.[4,9,10] Stanbury[9,10] and Dent[4] have amply demonstrated this resistance, but the exact cause of it is unknown. When this occurs, there is impaired absorption of calcium (and secondarily of phosphorus) from the gastrointestinal tract, the development of rachitic or osteomalacic demineralization, and defective activity of parathyroid hormone on the skeleton. This sequence of events, particularly the latter, can lead to a fall in Ca^{++} in body fluids before there is a significant rise in the concentration of $PO_4^{\equiv}$. However, when the degree of renal impairment is great enough (usually to 25 per cent of normal[5]) to cause a rise in the concentration of $PO_4^{\equiv}$, this will contribute significantly to the fall in serum Ca^{++}. A decrease in the concentration of Ca^{++} will cause the characteristic secondary hyperplasia of the parathyroid glands. If the skeleton can respond to the sustained increase in the level of circulating parathyroid hormone, normal levels of Ca^{++} in the body fluids may be achieved, but at the expense of the development of varying degrees of osteitis fibrosa. A poor osseous response to parathyroid hormone would be associated with less bone disease but more pronounced hypocalcemia for any given elevation of serum $PO_4^{\equiv}$. Stanbury said that in patients with severe hypocalcemia (5 mg. per 100 cc. or less) radiographic evidence of hyperparathyroidism was definitely less than in patients with more normal levels of serum calcium.[9]

In the kidneys, unlike the skeleton, there is no evidence that the response to parathyroid hormone is impaired by vitamin D deficiency or resistance. The response is limited, however, by the degree of renal impairment or reduction in functioning nephrons. Nevertheless, under the influence of the

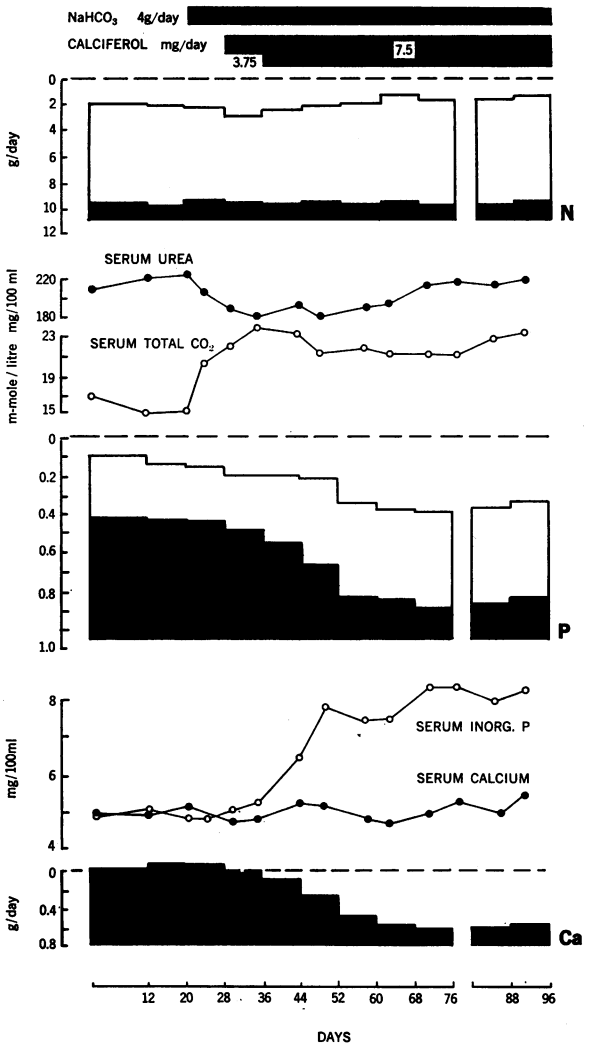


Chart 2.—The effect of calciferol on calcium and phosphorus balance and the concentration of calcium and inorganic phosphorus in the serum. Intake is recorded from the zero line down, output from the intake line up. Black area represents fecal output and grey area represents urinary output. Note that despite the strongly positive balance of calcium, serum calcium did not rise. The positive balance of phosphorus was accompanied by a progressive increase in serum phosphorus. (From Stanbury,[9] with permission of the author.)

increased circulating level of parathyroid hormone, the residual renal tubules would reabsorb a greater amount of the filtered calcium[1,7,12] and a lesser amount of the filtered phosphorus. This is the pattern characteristically observed as chronic renal disease progresses.

The scheme presented in Chart 1 allows the formulation of a reasonable approach to therapy. Obviously, if the course of the chronic renal disease can be slowed or reversed, this should be attempted. Frequently this is not possible. Vitamin D resistance and its metabolic consequences must be treated by adequate doses of vitamin D or dihydrotachysterol.

This may require 1 to 10 mg. (40,000 to 400,000 units) of active sterol. An adequate (1 gm.) but not excessive intake of calcium should be prescribed. If the concentration of phosphate in the serum is elevated before sterol therapy or, as frequently occurs, it rises decidedly during therapy (Chart 2), dietary restriction of phosphorus or the administration of aluminum hydroxide gels is indicated. An increasing serum $PO_4^{\equiv}$ can definitely prevent a rise in the calcium concentration of the serum, despite a good objective and subjective skeletal response to vitamin D (Chart 2).[9] Phosphorus restriction per se may, by decreasing the concentration of serum $PO_4^{\equiv}$, cause a rise in the concentration of Ca^{++}. However, Stanbury and Dent[9] emphasized that the elevation of serum $PO_4^{\equiv}$ does not in itself cause the osteodystrophy, and Dent[3] noted that the phosphorus deficiency that may follow the administration of aluminum hydroxide gel may cause a worsening of the osseous disorder. Therefore, phosphorus restriction and aluminum hydroxide gels should be used, when necessary, in conjunction with vitamin D therapy to prevent a decided rise in serum $PO_4^{\equiv}$ concentration.

It has been suggested for some time, and confirmed by Stanbury,[9,10,11] that patients with normal concentrations of Ca^{++} in their serum despite pronounced elevation of serum $PO_4^{\equiv}$, have a severe degree of secondary hyperparathyroidism. In fact, Dent[3] observed a case of secondary hyperparathyroidism in which the level of ionized or free Ca^{++} in the serum was above normal. This certainly suggests a state of autonomous overactivity of the parathyroids. Stanbury observed that patients of this type may definitely benefit from subtotal parathyroidectomy, whereas the administration of vitamin D before parathyroidectomy may induce dangerous metastatic calcification. This latter point serves to emphasize that whenever vitamin D is used in the treatment of renal osteodystrophy the physician must be aware of the fact that the strikingly beneficial objective and subjective effects can be replaced by the hazardous signs of vitamin D intoxication and hypercalcemia.

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